EXHIBIT A

MEDICAL ONCOLOGY

Basic Principles and Clinical Management of Cancer

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The oncologist should adhere to certain general principles of management to provide patients with the best possible care. These principles can be divided into the following considerations:

1. Establishment of the diagnosis
2. Determination of the extent of disease
3. Curative versus palliative therapy
4. Establishment of recurrence after potentially curative therapy
5. Supportive care
6. Record keeping and communications

These subjects are discussed, in more or less detail, in chapters that deal with specific disease sites, treatment modalities, and areas of supportive care. This is a general overview expressing the editors' principles of management.

The essential starting point in any case is the establishment of the diagnosis of cancer by a competent pathologist. The majority of patients are referred to the medical oncologist after a diagnosis of cancer has been made or is strongly suspected. The diagnosis of cancer, and the determination of the type of cancer, cannot be established without an appropriate biopsy and study by an experienced pathologist. There may be clinical presentations that make the diagnosis of cancer virtually certain, as well as the specific site of origin or histologic type, but despite these probabilities it is mandatory that an adequate biopsy be obtained. Increasingly disease-specific therapies are being developed that will have optimum application for only one tumor type, although representing ineffective and toxic treatment for others. It is also highly inappropriate to employ the therapeutic modalities for cancer in patients who have benign disease but who, for lack of adequate biopsy material, are presumed to be harboring a neoplasm.

Rarely, a therapeutic program must be initiated without a tissue diagnosis of neoplasia. Life-threatening situations may precipitate such a choice, one in which an invasive procedure required for biopsy is thought to be more dangerous than the treatment itself, in a setting where the clinical evidence is virtually diagnostic of a particular neoplasm. As an example, this situation may occasionally arise in the presence of an intrathoracic tumor with superior vena caval obstruction, airway obstruction, or pericardial tamponade; with intracerebral tumors; tumors of the spinal cord; and perhaps others. Even in these settings, however, in the great majority of instances, an adequate biopsy can be obtained.

The oncologists should be confident that the best possible pathologic diagnosis has been obtained. Whenever possible, a formal signed pathologic report should be reviewed before proceeding with a management program. It is often very desirable to have a second pathologic opinion for difficult cases and for diagnoses that are in acknowledged areas of controversy. Most pathologists are willing and accustomed to exchanging slides and tissue blocks among their colleagues.

One of the most difficult clinical problems encountered by the medical oncologist is the newly diagnosed patient with a neoplasm of unknown origin. In some patients the primary site of disease will not be identified, despite the initiation of an exhaustive and costly diagnostic evaluation. Many studies have shown that this group of patients has, in general, a very

Table 10-2. Neoplastic Diseases Responsive to Chemotherapeutic Agents

CLASS	TYPE OF COMPOUND	AGENT	DISEASE*
Alkylating Agents	Nitrogen mustards	Nitrogen mustard	Hodgkin's disease
		Cyclophosphamide	Chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, breast, ovary, and lung
		Melphalan	Multiple myeloma, breast and ovary
		Chlorambucil	Chronic lymphocytic leukemia, Waldenström's macroglobulinemia, non-Hodgkin's lymphomas
	Alkyl sulfonates	Busulfan	Chronic granulocytic leukemia
	Nitrosoureas	Carmustine (BCNU)	Hodgkin's disease, non-Hodgkin's lymphoma, primary brain tumors, multiple myeloma
		Lomustine (CCNU)	Hodgkin's disease, non-Hodgkin's lymphoma, primary brain tumors, and small cell lung
		Somustine (MeCCNU)	Primary brain tumors, stomach and colon
		Streptozotocin	Islet cell tumors of the pancreas, carcinoid
	Triazenes	Dacarbazine	Hodgkin's disease, soft tissue sarcomas, melanoma
	Antibiotics	Mitomycin	Stomach, breast, cervix, lung, pancreas, head and neck
Antimetabolites	Folic acid analogs	Methotrexate	Acute lymphocytic leukemia, choriocarcinoma, mycosis fungoides, osteogenic sarcomas, breast, head and neck, lung, leukemic and carcinomatous meningitis
	Pyrimidine analogs	5-Fluorouracil	Colorectal, breast, ovary, stomach, bladder and pancreas
		Cytosine arabinoside	Acute myelogenous and acute lymphocytic leukemias, leukemic and carcinomatous meningitis
		5-Azacytidine	Acute myelogenous leukemia
	Purine analogs	6-Mercaptopurine	Acute lymphocytic leukemia
		6-Thioguanine	Acute myelogenous leukemia
	Substituted urea	Hydroxyurea	Chronic myelogenous leukemia, polycythemia vera, essential thrombocytosis, acute leukemia with high blast counts, head and neck, colon and cervix, and the hypereosinophilic syndrome

Adapted from Calabresi, P., and Parks, R. E., Jr.: Chemotherapy of neoplastic diseases: Introduction. In Gilman, A. G.; Goodman, L. S.; and Gilman, A. (eds.): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed. Macmillan Publishing Company, New York, 1980.

* Neoplasms are carcinomas unless otherwise indicated.

Table 10–2. Neoplastic Diseases Responsive to Chemotherapeutic Agents (Continued)

CLASS	TYPE OF COMPOUND	AGENT	DISEASE*
Natural Products	Vinca alkaloids	Vincristine	Acute lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, and breast
		Vinblastine	Testicular tumors, Hodgkin's disease, non-Hodgkin's lymphomas
		Vindesine	Chronic myelogenous leukemia, blastic phase; non-Hodgkin's lymphomas, systemic mastocytosis
	Epidophyllotoxins	Etoposide (VP-16-213)	Acute myelogenous leukemia, small cell lung, non-Hodgkin's lymphomas, testicular tumors
		Teniposide (VM-26)	Hodgkin's disease
	Antibiotics	Doxorubicin	Hodgkin's disease, non-Hodgkin's lymphomas, soft tissue sarcomas, acute lymphocytic leukemia, hepatoma, breast, lung, stomach, ovary, thyroid, pancreas, endometrium, and bladder
		Daunorubicin	Acute myelogenous leukemia
		Bleomycin	Testicular tumors, Hodgkin's disease, non-Hodgkin's lymphomas, head and neck, cervix, esophagus, skin, vulva, and lung
		Actinomycin D	Wilms' tumor, embryonal rhabdomyosarcoma, choriocarcinoma, Ewing's sarcoma, Kaposi's sarcoma, and testicular tumors
		Mithramycin	Hypercalcemia, testicular tumors
	Enzymes	Asparaginase	Acute lymphocytic leukemia
Miscellaneous Agents	Platinum coordination complexes	*cis*-platinum	Testicular tumors, head and neck, ovary, bladder, thyroid, uterine cervix, and lung
	Methyl hydrazine derivative	Procarbazine	Hodgkin's disease, lung cancer, primary brain tumors
	Adrenocortical suppressant	Mitotane	Adrenal cortex
Hormones and Antagonists	Adrenocorticosteroids	Prednisone; several other equivalent preparations	Acute and chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, breast
	Progestins	Hydroxyprogesterone caproate; medroxy-progesterone acetate; megestrol acetate	Breast and endometrium
	Estrogens	Diethylstilbestrol; ethinyl estradiol; other preparations	Breast and prostate

Table 10–2. Neoplastic Diseases Responsive to Chemotherapeutic Agents (Continued)

CLASS	TYPE OF COMPOUND	AGENT	DISEASE[a]
Hormones and Antagonists	Androgens	Testosterone propionate; fluoxymesterone; other preparations	Breast
	Antiestrogen	Tamoxifen	Breast

ALKYLATING AGENTS

The leukopenia and toxicity to lymphoid tissues observed following exposure to sulfur mustard in World War I prompted the laboratory studies that demonstrated the tumoricidal activity of nitrogen mustard to a murine lymphosarcoma. Activity against human cancers was initially shown in 1943 when a patient with Hodgkin's disease obtained a dramatic response after the administration of nitrogen mustard. Since that time, the diverse group of compounds with alkylating activity has proven useful in the treatment of a wide variety of neoplastic and non-neoplastic diseases (Gilman, 1963).

Many compounds with structural similarities to the nitrogen mustards have been synthesized, but only a few are clinically effective antitumor agents (see Figure 10–3). Five major classes of alkylating agents have been used in cancer therapy: (1) the nitrogen mustards, (2) the ethylenimines, (3) the alkyl sulfonates, (4) the nitrosoureas, and (5) the triazenes. The antibiotic mitomycin C also functions as an alkylating agent.

Biochemical Pharmacology

Chemically and functionally, the alkylating agents are characterized by the ability to form covalent bonds with nucleophilic, electron-rich, regions on biologically important macromolecules, such as nucleic acids and proteins (Ludlum, 1967; Rhaese and Freese, 1969; Bannon and Verly, 1972; Colvin, 1982). Phosphate, amino, sulfhydryl, and hydroxyl groups are frequent sites of attack. The most important target of the alkylating agents is the DNA molecule. Alterations of the structural integrity and function of DNA result in the cytotoxicity, mutagenicity, and carcinogenicity associated with these compounds.

The generation of an active alkylating species from the parent compound is most often mediated through the formation of a positively charged carbonium ion. For the chloroethyl alkylating groups, this is accomplished by an intramolecular cyclization and formation of an unstable ethylenimonium intermediate. Spontaneous opening of the ring then produces the active carbonium ion.

Any free oxygen and nitrogen in the purine and pyrimidine bases of DNA are targets for alkylation, the 7-nitrogen position of guanine, however, is particularly vulnerable (Brookes and Lawley, 1961; Lawley and Brookes, 1963). The 1-nitrogen and 3-nitrogen positions of adenine, the 6-oxygen position of guanine, and the 3-nitrogen position of cytosine are other

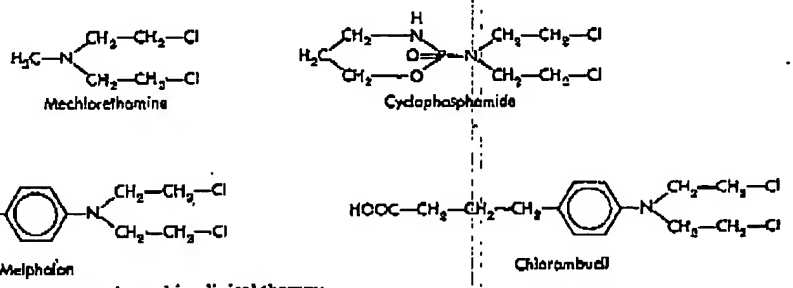

Figure 10–3. Nitrogen mustards used in clinical therapy.